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Review

Quality and functionality of excipients

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Abstract

The quality of medicines depends not only on the active principles and production processes, but also the performance of the excipients. The traditional concept of the excipient as any component other than the active substance has undergone a substantial evolution from an 'inert' and cheap vehicle to an essential constituent of the formulation. The rapid evolution of scientific, regulatory and economic factors, the introduction of delivery systems and the advance in biopharmaceutics have led to a new interest in the role and functionality of the excipients. More than one thousand raw materials are available from a multitude of sources and are used today in the pharmaceutical industry. Their chemical structures vary from small molecules to complex natural or synthetic polymeric mixtures. Excipients are now chosen to perform a variety of functions to guarantee the stability and bioavailability of the drug substance from the drug product and its manufacturability on a production scale. Beyond the dosage form necessities, excipients are required to perform important and specific technological functions, particularly in the case of solid dosage forms. As a consequence, their characterisation must go beyond the simple tests for identity, purity and strength as prescribed in general by the Pharmacopoeia monographs. With the exception of the Textbook of Pharmaceutical Excipients, not many reference sources describing the physical mechanical characteristics of the powders for a specific role are available. Full physical characterisation of solid materials is now made possible with the help of high resolution analytical techniques on the molecular, particulate and bulk levels. This systematic approach is necessary to guarantee the behaviour of the excipient during the formulation and production phases. Some examples have been chosen in this mini-review in an effort to highlight the emerging trends in the development of 'tailor-made' materials. Three main approaches are followed by the industry: physical or minor chemical manipulation of materials already known, combination of two or more marketed excipients in order to reduce unwanted defects and, finally, preparation of new chemical entities with huge investments for the toxicity studies. Excipient harmonisation, standardised functionality tests, preformulation data bases and expert systems will contribute to change the conventional trial-and-error formulation approach into a far more scientific and technological development.

Keywords: Excipient performance; Pharmacopoeial standards; Solid material characterisation; Pregelatinised starch; Microcrystalline cellulose; Amorphous lactose

1. Evolution of the concept of the excipient

1.1. Traditional concept of the excipient

The biological and analytical requirements necessary for the registration of an active principle as a medicinal speciality, whether of natural or synthetic origin, have always been at the centre of the pharmaceutical industry's and health authorities' attention [1]. Ever increasing demands and expectations with regard to quality have stimulated the development of new drugs characterised by higher assay and lower content of impurities [2]. However, the quality of a drug does not depend only on the characteristics of the active substances and the production process but also partly on the quality of the excipients. In general, the latter contributes notably

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to the performance of the drug and this, contrary to what was believed in the past, is fundamental to guarantee the safety and efficacy of the final pharmaceutical product [3]. Confirmation of this 'historical' under-estimation of the role played by the excipient is already discernible in the definition of the *traditional concept* which saw it simply as a substance that facilitates the administration and preservation of the active principle.

Some factors outside the pharmaceutical sector, such as the supply sources, the quality of the material, the manufacture and marketing of raw materials (Table 1) justify, at least in part, the scant attention paid to the matter of excipients up to a few years ago. This attitude was also engendered by the very low incidence of the cost of the excipients in the global cost of the compound, often lower than 1%. On the other hand, if we take into consideration the composition of a medicinal product from the point of view of its weight, it will be noted that the percentage of the active principle contained in the formula is generally considerably lower than that of the excipients. In the three drugs shown as examples in Table 2, the weight of the active principle varies from a maximum value of 12% in the formulation of sugar-coated tablets, to 0.5% in drops, to the lowest content of 0.0008% in the preparations for ampoules. These percentages become simply infinitesimal if homeopathic preparations are taken into consideration, seeing that they are obtained from successive dilutions of thousandths from the parent tinctures [4].

From the chemical point of view, even the so-called *inertia* of the excipients is to be accepted with reservations. In fact, like active principles, excipients have their own internal thermodynamic energy. This results in a certain reactivity which, though low, may, when influenced by chemical and physical factors in the environment, trigger some reactions leading to degradation, with fortunately usually slow kinetics. In the formulations in Table 2 there are some excipients containing reactive organic functions such as ethyl alcohol and propylene glycol, the terpenic essences in flavourings, iodised colourings, iron oxides and complexing (ex. EDTA) and reducing substances such as lactose. Considerable percentages of chiral excipients (starch, cellulose) are also employed and these may react with racemic active principles due to the law of mass, giving rise to diastereoisomers endowed with different chemical properties and therefore different bioavailability [5].

Another fundamental characteristic of the classical excipient, besides its so-called chemical inertia, is its *pharmacological and toxicological inactivity*. One cannot generalise in this case either when one thinks of the use that has been made of ethanol and boric acid, sulfites and tartrazine with their immunological effects, organic mercury compounds and some mineral oils, not to mention the psychological effects of excipients as *placebos*.

From these preliminary remarks it is clear that the two traditional requirements of an excipient, inertia and pharmacological and toxicological inactivity, are not always met. The supposed inertia of an excipient is often more of an expectation than the result of a real thermodynamic paralysis. Only a thorough study in the

Table 1
The traditional excipient

Source	From a multitude of natural sources, in general as a complex mixture of similar compounds, and from synthetic polymers.
Production	For chemical, food, agricultural and cosmetic industries, partly and not particularly, for the pharmaceutics industry.
Quality	Often not suitable for pharmaceutical use, tested by the consumer, not by the manufacturer, physical properties not qualified as excipient.
Market	Raw materials for commercial scale productions, with limited grade offered, low price and no trademark.

Table 2
Weight ratio between active principle and excipients

Valium®2 guttae		Laroxyl® pills		Turbocalcin® vials	
Diazepam	mg 5	Amitriptyline	mg 11	Carbocalcitonin	μg 8
Colourant E 127	to ml 1	Colourant E 172	mcg 500	Turbocalcin vials	to ml 1
Alcohol	100	Starch	10.6	Sodium chloride	mg 7.5
Propyl glycol	600	Lactose	17.5	Sodium acetate	2
Saccharin	11.4	PVP	0.9	Acetic acid	
Orange ess.	20	Magnesium stearate	4.1	W.F.I	to ml 1
Lemon ess.	10	Gum arabic	1.1		
Colourant E 127	9.2	Ethyl cellulose	0.3		
Water	to ml 1	Colorant E 172	mcg 25		
		Titanium oxide	mcg 500		
		Paraffin	14		
		Sucrose	to 90		
Ratio = 0.5%		Ratio = 12%		Ratio = 0.0008%	

preformulation phase will show which are the most suitable excipients, clarify their reciprocal interactions and evaluate their real contribution to the efficacy of the medicinal product [6].

1.2. The excipient as adjuvant agent

The majority of pharmaceutical dosage forms falls into the category of solid, semi-solid and liquid disperse systems, in which the active principle/s are considerably diluted, as we have seen. The excipients have therefore to carry out the functions of diluent, filler and solvent so as to give the dose of active principle suitable *weight, consistency and volume* from the galenic point of view, and make it more convenient to administer [7]. In this case, the excipient assumes the function of *vehicle* suitable for the desired administration route, so as to transport the active principle to the desired place of absorption in the organism. The study and creation of more or less complex disperse systems require a sufficient knowledge of physical chemistry and physics to be able to assess their contribution to the stability and release of the active principle.

Besides the traditional functions of support and vehicle therefore, the excipient is also expected to function as an *adjuvant*, from the Latin verb '*adjuvare*', that is to help the active principle to carry out its activity by conditioning its release from the pharmaceutical dosage form. In the National Formulary Admission Policy of 1994 [8] there is the following definition: "Excipients are any component other than the active substance(s) intentionally added to the formulation of a dosage form." To interpret the adverb 'intentionally' in this definition, we must remember the main administration routes of a medicinal product and the complexity of the roles the excipient must play in their respective formulations [9]. For each of the administration routes indicated in Table 3, the excipient must guarantee the stability of the pharmaceutical dosage form, the precision and accuracy of the dosage, as well as modify, when necessary, its organoleptic characteristics (smell, taste, swallowability and local tolerability) so as to improve the patient's 'compliance'.

Table 3
The excipient in modern formulations

Routes of administration	Rôles to enhance
Oral	Organoleptic properties
Rectal and vaginal	Compliance
Inhalation	Dose precision and accuracy
Topical	Stability
Transdermal	Side-effects
Intraocular	Desaggregation, dissolution
Intranasal	Controlled release
Parenteral	Absorption

To these traditional rôles are added today those of controlling and regulating the rate of disaggregation and dissolution, with possible favourable repercussions on the release profile of the active principle and its bioavailability, understood as the speed and amount of active principle released from the pharmaceutical dosage form and entering the systemic circulation. The pharmaceutical dosage form thus outlined can optimise the therapeutic efficacy of the medicinal product while simultaneously reducing its undesired side effects. The study of the formulation of a medicinal product on an empirical basis is now a thing of the past and Pharmaceutical Technique is gradually and inevitably changing from an Art (witness the italian initials FSA: fai secondo arte) into an Applied Science, which requires multi-disciplinary competence, as we shall see further on.

1.3. The evolution of excipients

From the standpoint of what we have said so far, the excipient is no longer to be considered an inert product but an essential and functional component of a modern pharmaceutical dosage form [10]. What are the external factors that have contributed to this evolution, not only in the concept but also in the regulations governing excipients? In Table 4 certain elements have been summarised so as to facilitate the understanding of the rapid and profound change in the characteristics and quality of excipients which has occurred since the 1970s and 1980s [11].

The globalisation of demand and economies of scale are the consequences of an industrial philosophy that rewards partnerships and mergers between pharmaceutical companies with the formation of important multinational companies enjoying considerable financial reserves. This enables them to support the basic and applied research activities necessary to innovate their range of products in the future. The organisation of work (*just in time*), too, and the size and scattered locations of the production plants are rapidly undergoing transformation and rationalisation so as to reduce as much as possible the time required for development and the number and variability of production batches. As a reflection of this, even the machinery, such as ampoule-fillers, tabletting and encapsulating machines, has to be re-designed so as to work at high speeds.

It follows that it is necessary to have at one's disposal new excipients that are compatible not only with modern processes and production machinery (rotating and not conventional tabletting machines, rotating granulators, compactors, etc.) but also with *innovative active principles* coming, that is, from biotechnologies and modern peptide synthesis [12]. Moreover, the interest in and wide-spread use of new therapeutic systems and modified-release forms is another factor that spurs the demand for more sophisticated excipients that can fulfil

Table 4
Factors impacting on the evolution of excipients

Scientific and regulatory factors	
National Formulary as exclusive Excipient Compendium	(1980)
Over 100 new monographs added to NF	(1975–1990)
NF Panel on Moisture Characterisation	(1985–1990)
USP/NF Special Advisory Panel in Physical Test Methods	(1991)
Int. Pharmac. Excipient Council (IPEC) Foundation	(1991–1994–1998)
Int. Pharmac. Excipient Council European Conference	(1994)
Eur. Pharmacopoeia Group of Experts to Test Functionality	(1995)
The Int. Conference on Harmonisation	ICH (1991), ICH 2 (1993), ICH 3 (1995), ICH 4 (1997)
Handbook of Pharmaceutical Excipients	I ed. (1986) II ed. (1995)
Technological and economic factors	
Higher productive power	(tablet presses with higher compaction speeds, non conventional rotary presses,...)
New excipients	(for novel and potent drugs, for biotechnology products, for controlled release formulations, for new delivery systems....)
Globalisation demand	(organisational restructuring, merging, just-in-time, automation,...)

specific functions within the formulation. These innovative formulations permit the optimisation of plasmatic concentrations of the active principle, thus increasing efficacy, the patient's compliance and the added value of the medicinal product [13].

The scientific and regulatory events that have contributed to the evolution of the excipients sector over the last twenty years, in concomitance with the economic and technological factors, are not to be neglected. Returning to the situation in the past, excipients were taken from materials of natural origin and in common use in the chemical and agricultural food-stuffs sectors and employed in the pharmaceutical field just as they were, without further purification to improve the assay or their chemical or physical characteristics. Analytical tests were conducted for the most part within the Pharmaceutical Industry and not by the supplier of the raw material. The tests were often limited and not sufficient to characterise the excipients' quality, much less their functionality. To give a few examples, only one type of 'spray-dried' lactose was available for the production of tablets and capsules by direct compression. Magnesium stearate was widely employed as a lubricant, even though there was scant knowledge of its structure and lubricating capacity. Since 1970, the situation has evolved swiftly under the pressure of new knowledge of the solid state of materials and the ever more stringent qualitative requirements demanded by the Regulatory Authorities.

Table 4 lists some scientific events, such as the inclusion of over a hundred monographs on excipients in the US National Formulary and the publication of two editions of the 'Handbook of Pharmaceutical Excipients', which contains monographs that meet pharmaceutical technologists' needs much more closely [14]. Furthermore, at the beginning of 1990, the Secretaries of the three most important Pharmacopoeias, the USP, the Eur. Ph. and the J. Ph., agreed on the importance of harmonising the standards and the testing methods regarding excipients, so as to satisfy the requirements of the industry and their own respective Regulatory Agencies. Considerable progress has been achieved since 1990 (Table 4) as a consequence of a good four Joint Pharmacopoeial Open Conferences on International Harmonisation of Excipient Standards and four ICH (Brussels, November 1991; Orlando, October 1993; Yokohama, November 1995; Brussels, 1997). The monograph on lactose monohydrate has reached the last stage of publication and those on magnesium stearate, saccharose, polyvinylpirrolidone as well as powdered and microcrystallised cellulose are at advanced stages in the procedure [15,16]. Some testing methods on the physical state, such as particle size, specific superficial area, poured and tapped density are also in an advanced phase of joint compilation.

The renewed interest in modified release forms and in new therapeutic systems, as well as new production technologies, has contributed, as already mentioned, to research into new materials endowed with specific technological properties and their development as functional excipients. All these factors and more have changed the traditional concept of an excipient into the more up-to-date one of *functional agent*, that is, one that can fulfil several functions within the pharmaceutical formulation. They have also contributed to focusing the pharmaceutical technologists' attention on the quality of the excipient, which also contributes to the efficacy and safety of use of the medicinal product, together with that of the active principles.

2. Functions and specifications of excipients

2.1. Functions of excipients

On the basis of the preceding considerations, it is clear that excipients are no longer to be considered as

Table 5
Modern excipient functions

Stability	Drug absorption
Antioxidants	Disintegrants
Chelating agents	Plasticisers
Preservatives	Drug release modifiers
Stabilisers	Penetration enhancers
Buffers	Wetting agents, solvents
pH modifiers	Film formers
	Bioadhesives
	Encapsulating agents
	Biodegradable polymers
Manufacturability	
Dosage form necessities	Specific techn. Properties
Ointment bases	Emulsifying, suspending ag.
Semisolid excipients	Gelling agents
Diluents,...	Lubrication enhancers
	Flow, compaction enhancers
	Propellents, bulking agents,...

inert materials but essential components of ever more sophisticated and modern pharmaceutical dosage forms. Excipients are employed to carry out different functions that may be grouped into three categories, according to whether they influence stability, release and absorption of the active principle or manufacturability during the manufacturing process phase [17]. Excipients with this latter function may be subdivided in turn into those that are basic components of a certain pharmaceutical dosage form (dosage-form necessities), such as ointment bases, or into a second sub-group of materials that can fulfil particular technological functions, such as lubricants (Table 5). Thus, by varying the type, quantity and quality of the excipient incorporated, the pharmaceutical technologist can correct and optimise the characteristics of the final formulated product.

In the case of the manufacture of tablets and hard capsules, for instance, modern excipients must be suitable for the preparation of homogeneous and flowable mixtures during the intermediate manufacturing process of the powders and granulates, so that the modern tabletting and encapsulating machines are fed swiftly and smoothly. In order to fulfil the multiple functions shown in Table 5, the specifications of modern-day excipients must add a series of technological functional measures to the normal characterisation of analytical purity [18,19]. The technological tests of physical chemistry and mechanical physics are drawn up schematically in Table 6 and are as important today as the traditional tests that were carried out to ascertain the analytical identification, assay and purity of the active principle.

2.2. Pharmacopoeial monographs and their limitations

Confirmation of the gaps in the analytical specifications of excipients may be gathered from reading the monograph on ***magnesium stearate*** (*magnesium stearicum*) in the Italian Official Pharmacopoeia IX Edition [20], where the following tests are prescribed:

- Composition: mixture of variable and unspecified proportions of magnesium stearate, palmitate and oleate.
- Title: Mg between 3.8 and 5%.
- Organoleptic characters: very fine powder, white, oily...
- Solubility: practically insoluble in water, ethanol and ether.
- Identification: melting point of organic residue, characteristic reactions of magnesium.
- Assays: colorimetric comparison of solution S with a comparable solution, appearance of chloroform solution of fatty acids.
- Acidity or alkalinity: blue indicator of bromothymol.
- Acidity index of fatty acids: between 295 and 210.
- Chlorine, sulfate and heavy metals test: within the limits.
- Loss on drying: equal to or lower than 6% at 100–105°C.

The *quantitative determination* prescribes the complexometric titration of magnesium with zinc sulfate and sodium edetate.

Table 6
Modern excipient specification

The tests on the functionality of the excipients comprehend:

Control of purity

Chemical characterisation: identity, purity, strength, composition

Control of performance

Physical characterisation:
describes the functional attributes that make the excipient perform (why the excipient does what it does)

Physico–mechanical testing:
relates to a specific application (what the excipient does)

Excipient specifications thus ensure the dosage-form necessities:
Safety, Stability, Absorption, Manufacturability

The method employed to produce the raw material is not requested, the purity test employs dated analytical methods and totally absent are the testing of the physical chemistry, physical and functional parameters, which characterise the mechanical physical performance of the lubricant.

These shortcomings in the Pharmacopoeia's monographs (F.U.I. IX Ed., N.F., and others) are no longer acceptable because it has been demonstrated that chemically similar materials do not always give the same results during the manufacturing phase. For greater clarity, Table 7 lists some of the parameters of magnesium stearate that it is important to know so as to assess its efficacy as a lubricant. It is to be noted that this excipient can be produced industrially in widely differing crystalline forms and sizes by melting and milling or by precipitation in an aqueous suspension [21].

The above-mentioned shortcomings are also repeated in other monographs on excipients in the F.U.I. IX Ed. as, for example, in those on ***lactose*** (*lactosum*), which do not go beyond the usual approximative description of the characteristics, the solubility in water and alcohol of its organic and inorganic impurities (proteins and Pb respectively) and instead emphasises the aspects concerning identification and assays (acidity, water content, specific rotation capacity and bacterial contaminants). But to which lactose do the monographs refer? There are several types of lactose on the market: monohydrate, anhydrous, spray-dried; they are listed in Table 8 together with the principal characteristics that modify the functionality of this excipient [15].

These two examples of widely-used excipients confirm that verification against the traditional monographs is not sufficient, because the latter are based to too great an extent on simple identification tests and often outdated chemical assays for purity, with no sort of testing of the functionality of the excipient itself. Furthermore, the up-dating of the monographs relating to the excipients more recently used is not timely [22]. This type of 'traditional' specification is therefore not suitable to discriminate between batches of similar purity but with different characteristics in the solid state, such that can modify the processability and behaviour of the intermediate and final formulation. The consequent problems concern the variability from one batch to another, the inadequate knowledge of the formation of the solid particles and their interactions. The traditional methods to test the physical properties also depend on the type of technique employed and often give results that cannot be compared from one laboratory to another. There are also no screening methods for materials that are sensitive to the conditions prevailing during the formulation process.

Table 7
Lubricant activity of magnesium stearate

Manufacturing methods	Melting of the starting materials Precipitation in an aqueous suspension of fatty acids and Mg salts
Milling	Breaks the crystal structure
Polymorphism	Anhydrate, dihydrate,...
Purity	Pure or mixtures
Particle size and shape	Layered plates or flakes, 1.5–13 μm
Bulk density	0.25–0.45 g/ml
Specific surface area	1–5–54 m^2/g
Moisture content	Lod: ≤0.5% at 80°C
Blending time	Dissolution decrease

Table 8
Lactose functionality

Single compound	Galactose–glucose disaccharide
Optical activity	Dextrorotatory 54.4–55.9°
Types	α-Monohydrate, α-anhydrate, β-anhydrous
Manufacturing methods	Spray-drying, roller drying,...
Particle size distribution	50–400 μm
Specific surface area	0.35–1.0 (m^2/g)
Density	1.540 (α); 1.589 (β)
Loss on drying (lod)	0.1–0.5% at 80°C for 2 h
Water test	1% for monohydrate and modified lactose
Crystallinity degree	Amorphous form may be present
Volatile impurities (ovi)	If organic solvents are used

3. Characterisation of excipients in the solid state

3.1. Physical properties of excipients

Given the numerous and complex functions that a modern excipient must fulfil, its characterisation must go well beyond the simple tests for identity, purity and titre as prescribed in the Pharmacopoeia monographs in general, and be extended to testing the technological functionality of the material, which is usually employed in the solid state. By *functionality* we mean the physical, physicomechanical and biopharmaceutical properties. This testing is complicated by the fact that excipients are not generally made up of single chemical entities but comprise more or less complex mixtures of polymers and synthetic and semi-synthetic natural derivatives designed for multiple uses in, for instance, food-stuffs, cosmetics and pharmaceuticals.

Considering the clear prevalence of solid forms in the pharmaceutical armamentarium, particular attention ought therefore to be paid to the study of excipients in the solid state at various levels of complexity: molecule, particle and aggregate. In Table 9 the right-hand

Table 9
Characterisation of raw materials in solid form

Scale of scrutinity	Property grouping	Properties studied
Molecule	Molecular	Structure
	Solid state	Phase analysis
	Crystallographic	Polymorph./solvates
		Crystallinity
		Solubility
		Mechanical
Microcrystal		Particle size and shape
	Particulate	Surface
Particle		Dissolution
Particle assembly		Packing
	Derived bulk	Flow
Bulk powder		Compaction

column lists the properties that may be studied according to the increasing state of aggregation (crystal, particle or group of particles). The first column lists the analytical methods that can be used to examine the molecule, the microcrystal, the particle or the bulk powder as such, even though it must always be borne in mind that the properties of the single unit are obviously correlated with those of the aggregates [23]. The manufacturing methods (precipitation, crystallisation, nebulisation, freeze-drying,...) and the process variables (temperature, stirring, saturation,...) have a considerable influence on these properties of the material.

3.2. High-resolution analytical techniques

The recent improvements in high-resolution analytical techniques and in the science of materials, allow for the determination of even small differences in batches of excipients and active principles, even if they are equivalent from the chemical point of view. The characterisation of the solid state and the surface parameters [24] is therefore fundamental first to assess and then guarantee the behaviour of the excipient in the formulation and production phases. Of particular interest are infrared spectroscopy and nuclear magnetic resonance to determine the molecular structure and possible chemical interactions (Fig. 1). Calorimetry and, above all, TGA and DSC analysis are often adopted to clarify stability, compatibility, degree of crystallinity and transitions of phase of the excipients. The structure of the single crystal or the powder can be examined with absolute certainty by X-ray diffraction. The hygroscopicity of powders and the possible formation of hydrates are revealed by isothermic absorption tests.

Even though the theoretical basis necessary to predict the behaviour of solid excipients is not yet completely clarified, so that they could be designed to meet optimal requirements for a particular manufacturing procedure, it is possible, however, to plan a series of preliminary technological tests to supply useful information in the preformulation phase. For obvious reasons of economy, the tests selected and carried out will be only those that are indispensable for the formulator to overcome the difficulties encountered according to the type of formulation and the performance desired. Further, more sophisticated tests to examine the matter more deeply will be carried out only if necessary. In the preformulation phase it is indispensable to activate a first level of enquiry, such as chemical and spectroscopy tests on structure, composition, purity and polymorphism at the molecular level. Routine technological tests will then follow on the

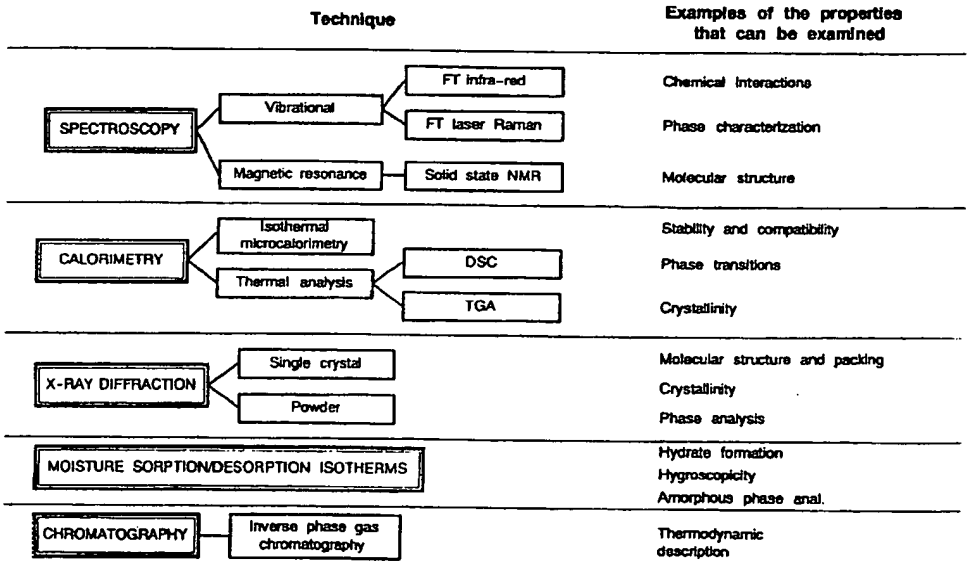

Fig. 1. High-resolution analytical techniques used for pharmaceutical excipients.

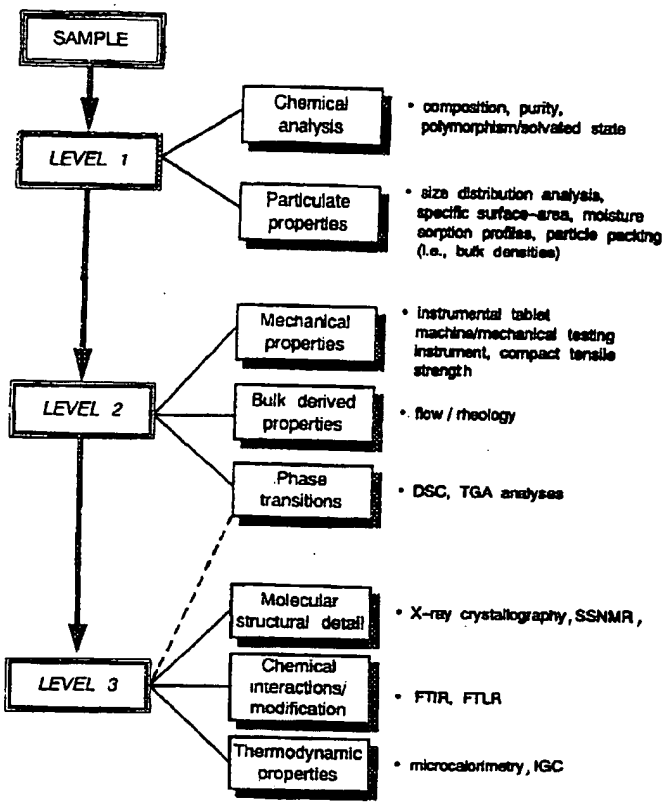

Fig. 2. Testing procedure for powdered raw materials.

granulometrics, specific area, density and tapped density at the particle level [25,26]. The upper levels 2 and 3 of Fig. 2 will be activated only when more exact information is required on the rheological and mechanical physical behaviour of the powders and aggregates in the particular manufacturing process and with a view to obtaining the optimal performance of the formulated product. A thorough understanding of the specific properties of a material can lead to indicating which of them will be crucial to the stability, good absorption and easy manufacturability of the formulation [27].

3.3. Influence of the properties of excipients on intermediate and final products

During the production process, the excipient's properties in the solid state, as well as those of the active principle, are reflected in the various parameters such as compressibility, flowability, fluidity, uniformity, lubrication, mixing and weight of the pharmaceutical dosage form [28]. In Fig. 3 the arrows indicate schematically how these properties of the powders and their aggregates will influence the uniformity of weight and content of the pharmaceutical dosage form, the hardness and speed of disaggregation of tablets, the chemical and physical stability of the formulated product, the coating of the active principle and, not least, its speed of release (bioavailability). As it is often difficult to foresee and determine technological functionality, it will be useful to start from the thorough physical characterisation of the excipient (establishing what it is) and proceed with a second step, if possible, to determine its behaviour (why it does what it does) by mechanical physical means.

4. Development of new functional excipients

The advancement of materials science and the availability of ever more sophisticated methods to characterise the solid state today, permit the design and development of a new series of excipients with 'tailor-made' characteristics for particular formulations and manufacturing processes.

A first approach in this sense, convenient from the point of view of economies of scale, consists in offering new types of material starting from the traditional excipients and modifying only some of their physical properties, such as particle size, and the degree and form of crystallisation. For example, magnesium stearate is still a widely-used lubricant even though there are three pseudopolymorphic forms (anhydrous, dihydrate and trihydrate) and even though it is its water content that is the main contributing factor to its lubricating action.

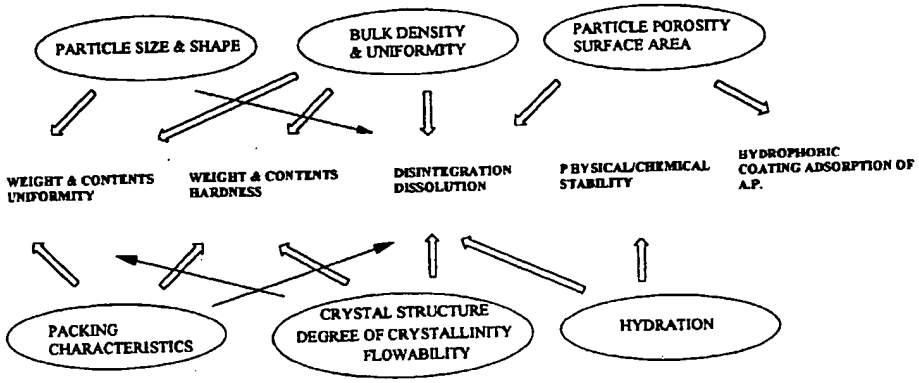

Fig. 3. Excipient and product properties.

It is the pharmaceutical technologist's task to select the most appropriate material based on the producer's specifications (*master file*) and in accordance with the requirements of the manufacturing process, bearing in mind not only the excipient's chemical purity but also its performance.

According to its origin, ***starch***, a polysaccharide of vegetable origin extracted from the caryopsides of numerous cereals, is categorised into one of the two polysaccharides that constitute it: amylose or amylopectin. For example, maize starch contains 27% of amylose whereas potato starch contains 22%. While amylose appears to be amorphous, amylopectin is described as partly crystallised in the ramified part of its structure [29]. The differences in content also change its physical properties, which means that the different starches may not be interchangeable as regards a specific pharmaceutical use. The characteristics of compressibility and flowability as well as the diluent, binding and disaggregating properties of this excipient have been improved by the manufacturers over the years in accordance with the performance requested, by means of a series of physical and/or chemical modifications of the natural product such as pre-gelatinisation and reticulation.

Among the derivatives that have acquired the most importance as excipients over the last few years, there are *the partially or totally pre-gelatinised starches*. These are obtained by submitting the starch to a chemical and/or mechanical treatment with water and successive drying aimed at totally or partially splitting the grains. When heated in an aqueous environment, the molecular order within the starch changes: the homogeneous and spherical grains of the natural product are transformed into very irregular particles in the gelatinised product. This product is amorphous and, when placed in water, has the advantage of dissolving or dispersing according to the concentration, even at room temperature. Although it has been included in the principal Pharmacopoeias (FUI II Suppl. 1991, USP, BP, EUPh. Suppl. 1998), pre-gelatinised starch has not yet been included in the international harmonisation project of pharmaceutical excipients. Furthermore, the present USP/NF monograph on pre-gelatinised starches is complete as far as purity requirements are concerned but is incomplete, as usual, with regard to their functionality. In fact, both partially and completely pre-gelatinised starch are found in the same monograph.

Starch 1500® is a partially (20%) pre-gelatinised maize starch comprising the three fractions: 5% free amylose, 15% free amylopectin and 80% untreated native starch [30]. The process of chemical and physical modification of starch breaks down some hydrogen bonds between amylose and amylopectin. The amylopectin therefore becomes readily soluble in cold water and enhances the binding properties of the product, whereas the superior disaggregating action is due to the amylose and the non-modified fraction of the starch. In this way, we obtain an excipient endowed with better self-lubricating qualities, suitable for direct compression.

Completely pre-gelatinised starches, such as *Lycatab PGS®* [31] are available on the market, and these have even further improved functional properties than the natural product. A comparative study [32] on the performance of these two types of pre-gelatinised starch used as binding agents in the wet-bed granulation of paracetamol tablets showed, among other things, better dissolution of the tablets formulated with completely pre-gelatinised starches (Fig. 4). Also available on the market today are *both chemically and physically modified* starches such as *Pregeflo-CH®*, composed of maize starch taken from the natural 'waxy' hybrid, selected for its high percentage of amylopectin. This is first reticulated (at several levels: CH-10, CH-20, CH-30) and then gelatinised and stabilised [33].

With the aim of revealing the different functional performance of starches, two batches of 300-mg tablets were produced by direct compression, under the same manufacturing conditions, containing either Pregeflo-CH® or Starch 1500® as diluent and paracetamol

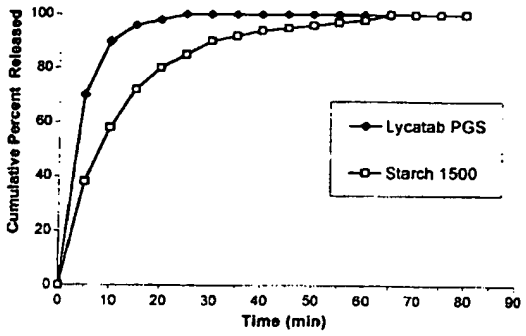

Fig. 4. Dissolution profiles of tablets containing different binders.

(60 mg) as the active principle, chosen for its poor flowability and cohesion, thus making it difficult to compact. The tablets produced with Pregeflo-CH® were seen to be harder and to have a slower disaggregation speed (over 30 min) and a longer dissolution time (Fig. 5) compared with those containing Starch 1500® (disaggregation within 10 min and complete release of the drug within 25 min). The dissolution profiles therefore indicate the potential use of Pregeflo-CH® as a diluent for direct compression in the formulation of slow-release solid pharmaceutical dosage forms.

Lactose, which is widely used as a diluent, is a disaccharide (*glucosium–galactosium*) naturally present in milk at a concentration of about 5%. In the form of α-lactose monohydrate it has a humidity content of 5%, it is stable in air and it is not hygroscopic; if it is dehydrated by means of organic solvents or heating, α-lactose anhydrous is obtained and this has a tendency to reconvert to its monohydrate pseudomorph when exposed to high relative humidity. β-Lactose, the anhydrous form of which is obtained from concentrated solutions of α-lactose at temperatures over 93.5°C, is essentially non-hygroscopic [34]. According to the USP/NF's definition, anhydrous lactose is first of all β-lactose or a mixture of α- and β-lactose anhydrous with under 1% humidity. The β-lactose available on the market contains an average of 70% β-lactose and 30% α-lactose [14]. In the international harmonisation process of pharmaceutical excipients, lactose, both hydrate and anhydrous, has reached level 7, the highest level of harmonisation.

From all the above, it is plain that as lactose is already present in nature under several forms, it is easy to modify both chemically and physically. For many years only crystalline α-lactose monohydrate was available on the market and, though with poor flowability, it is more compressible than the anhydrous form [27]. About thirty years ago, spray-dried lactose was developed, the first excipient designed specifically for the direct compression process, and it revolutionised tabletting production technology. Lactose which is obtained by spray-drying in the amorphous form improves the compactability and the tensile strength of the tablets when the moisture content (MC%) is increased (Fig. 6). This can be explained as a consequence of the increased deformability of the material due to the plasticising action of the water and the increased area of contact between the particles, which causes a variation in the forces binding them [35].

At the beginning of the 1970s, a new excipient called *Fast-Flo® lactose* was introduced. It was made of microcrystalline spherical aggregates of α-lactose monohydrate [36] and had better flow and compaction properties in order to improve the resistance of tablets produced with spray-dried lactose. Nowadays, the market also offers another excipient: *FlowLac 100®* made of very flowable spherical particles of partially amorphous spray-dried α-lactose monohydrate. FlowLac lactose offers better compaction properties than Fast-Flo lactose and has less tendency to capping: with the same compaction force applied and at pressures over 120 Mpa, the resistance to breakage of the tablets made with FlowLac is greater than that of the tablets made with Fast-Flo lactose.

The use of ***cellulose*** as a pharmaceutical excipient goes back to the 1950s, when *Solka-flock®* was intro-

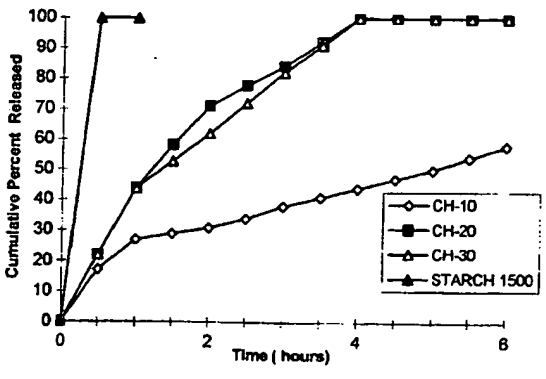

Fig. 5. Release of paracetamol from tablets compressed with different diluents.

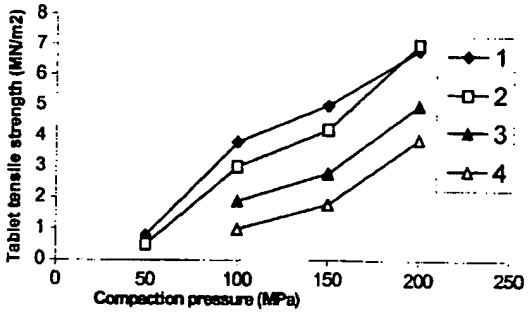

Fig. 6. Tensile strength of amorphous lactose tablets as a function of compaction pressure. MC% = 6.21(1); 4.30(2); 1.93(3); 0(4).

duced as a fine powder with diluent and disaggregating properties but with poor flowability and compactibility, which made it little suited to the direct compression process [37]. *Powdered cellulose* is produced by purification and mechanical reduction of α-cellulose obtained from wood pulp and has a degree of crystallinity of 15–45%. Numerous celluloses are available on the market, among which *Elcema*®, which is available as both a finely micronised powder (MFC microfine cellulose) and a granulate in several sizes, so it is also suitable for direct compression (G250) [38].

In order to improve the functional properties of this excipient, it was modified in several ways: the most important was that which led to obtaining *microcrystalline cellulose* (MCC), which is a partially depolymerised cellulose derived from a special type of α-cellulose, purified by means of strong acid hydrolysis to remove the amorphous cellulose fraction and produce particles in the form of groups of needle-shaped microcrystals [37]. The cellulose thus produced is washed, disintegrated into small fragments and then spray-dried in order to obtain a flowable and deformable powder [14]. This excipient is characterised by high crystallinity (60–80%) and lower molecular weight than MFC [39]. The degree of crystallinity in the cellulose is important because it influences the various properties including compactibility and absorption of water, which in turn influence flowability and the stability of the medicinal product. The chemical composition and physical structure of MCC depend significantly on the characteristics of the raw material employed and the manufacturing conditions [40]. As a result, several types of microcrystalline cellulose are available on the market with different crystallinity, granulometrics, morphology and water content and therefore with different functional parameters and applications.

The first MCC to appear on the market at the beginning of the 1960s, *Avicel*®, is still one of the most popular excipients in the manufacture of solid pharmaceutical dosage today. It can be used with all the different manufacturing methods for tablets but it is particularly suitable for the direct compression process because it has excellent compactibility and flowability together with self-lubricating properties. The particular structure of its crystals, with groups of long 'needles' that facilitate a natural mechanism of interweaving and reticulation, as well as the formation of hydrogen bonds between adjacent chains, give it excellent binding properties [41]. From the middle of the 1980s new cellulose products to compete with Avicel and meeting the requirements of the USP/NF for MCC, have been introduced on to the market. Among those more recently employed is *Vivapur*®, which is also available in several grades differing in granulometrics, degree of humidity and apparent density [42].

Comparing the flowability and compaction of Vivapur with those of the corresponding grade of Avicel, better performance was observed with the former product [43]. This superiority has been attributed to the different morphology of the Vivapur products, whose particles show a better capacity to fill empty spaces following compression and have a smoother surface because the cellulose fibres show less 'wispiness' at the ends. When using this excipient (MCC), low compression forces are sufficient to produce compactions that are resistant and yet elastic and with low friability. Following compaction, the particles deform plastically ('soft' behaviour) and draw closer together forming a hydrogen bond between adjacent molecules, giving rise to a particularly resistant compaction [37]. Despite this resistance, however, these compactions disintegrate quickly even though the microcrystalline cellulose is less efficient as a disaggregant than starch. Its suitability for tabletting manufacturing operations is therefore demonstrated by its numerous functions: diluent, disaggregant, (dry) bonding and spheronising agent in the production of pellets. Its high cost compared with that of other, more commonly employed, excipients, has caused it to be used in combination with other, cheaper, materials such as lactose, starch, mannitol, etc. Both powdered and microcrystalline cellulose are present in the most important Pharmacopoeias and it has reached the fifth level (5A) in the international harmonisation process of pharmaceutical excipients.

Combinations of two or more excipients are often employed in the pharmaceutical field to enhance the requirements of the single components and eliminate possible defects. The final properties of the materials thus obtained also depend on the technology used in their production: simple mixing or agglomeration by means of sprays.

Cellactose®, which has been on the market since 1990, is an example of this category of excipient. It is obtained [44] by co-processing α-lactose monohydrate (75%) with powdered cellulose (25%) by a special process, which leads to achieving one-body-compound with granular shape (agglomerate) suited to direct compression. The functional properties of Cellactose® are superior to those of the simple physical mixture of lactose and cellulose (Fig. 7). The advantages are evident both as regards flowability, which is seen from its angle of repose at 33° as compared with 49° for the mixture, and as regards its characteristics of cohesion and compactibility. These latter are the result of the synergic action of the consolidation mechanisms: fragmentation and plastic deformation, related to the two components, which occur during the compaction phase [45]. The tablets manufactured with Cellactose® show a high resistance to breakage, which is also independent of the variables of the manufacturing process, such as the speed of compaction and the length of time the punches are in contact with the material. A

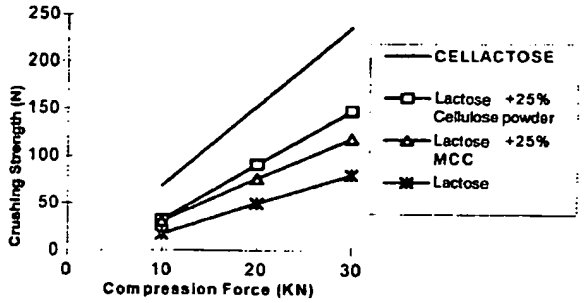

Fig. 7. Crushing strength vs. compression forces of Cellactose® tablets.

further advantage is that the machinery wears away less, since harder tablets can be obtained with less pressure. Despite this hardness, however, good disaggregation and reduced friability are assured.

Ludipress® is another example [46] of excipient suited to direct compression. It is obtained from the mixture of lactose monohydrate (93%), which provides the volume, Kollidon®30 (3.5%), which acts as a binding agent, and Kollidon®CL (3.5%), which acts as a disintegrating agent. This excipient, which comes in a granular form, has good flowability, good binding capacity and permits the production of hard but rapidly disaggregating tablets.

An alternative to modifying the physical properties of an excipient lies in altering the *chemical structure* of the material, as in the case of *sodium stearyl fumarate* [47]. This modern excipient is supplied in homogeneous and repetitive batches with more accentuated hydrophilic characteristics than magnesium stearate. Its lubricating power remains more constant for longer as compared with the latter and this means lower variability in the tablets' hardness in relation to the mixing time and the speed of dissolution (Fig. 8).

Products based on dextranomer and cadexomerum iodum are employed to absorb the exudates from suppurating sores. Both these polymers are prepared by reaction with epichlorohydrin, which is well known to be toxic. Microspheres of gelatine reticulated with glyceraldehyde have been described recently. This is a natural product from sugar metabolism that eliminates the problems of toxicity arising from the use of classical 'cross-linking' agents such as epichlorohydrin, formaldehyde and terephthaldehyde [48]. The swelling capacity and absorption of liquid of these microspheres are superior to those of the above-mentioned polymers, with favourable promise of use in the treatment of exudating sores, wounds and ulcers. Obviously, new chemical entities require considerable investment to complete the necessary toxicity studies [49], which are very similar to those required for the registration of new medicinal products.

A last and well known example of a new excipient is β-cyclodextrin, a cyclic oligomer of β-1,4-D-glucose, already known in 1890, and its analogues. Cyclodextrins have recently found new employment as complexants of active principles, with the aim of improving solubility, stability and absorption [50,51].

5. Conclusions

The traditional concept of excipient has undergone considerable evolution: from simple, chemically and pharmacologically inert vehicle to essential adjuvant, guaranteeing and optimising the performance of a modern medicinal product. In the past, the attention of the pharmaceutical industry and the Regulatory Authorities was directed mainly to controlling the quality of the active principles rather than that of the excipients. However, the rapid evolution of technological, economic, scientific and regulatory factors has meant that proper consideration is being paid again to the rôle played by the quality of excipients, including their physical characteristics and manufacturability as well as their importance in the formulation and manufacturing phases and for the release of the active principle. A new science, biopharmaceutics, the knowledge acquired on the solid state and the availability of sophisticated

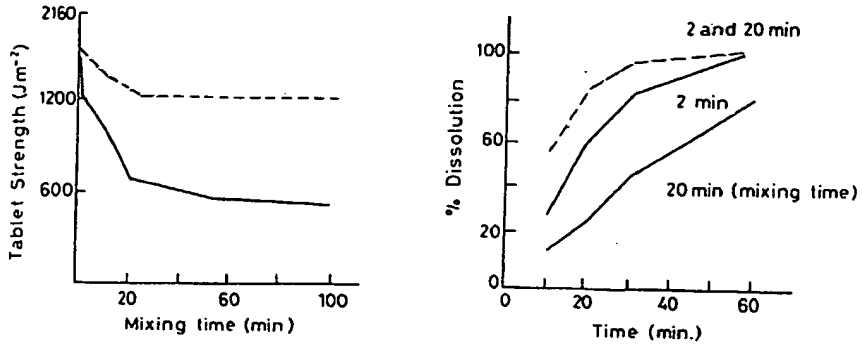

Fig. 8. Comparison between Mg-stearate (MS) and Na-stearyl fumarate (SSF). Left: — MS 0.5%, - - - SSF 0.5%; right: — MS 2%, - - - SSF 2%.

analytical technologies today enable the pharmaceutical technologist to design the most suitable formulation to improve the therapeutic efficacy of a medicinal product with art and method. It is now universally accepted that modern excipients must be considered an essential constituent of pharmaceutical dosage forms and they are therefore the object of the formulator's most careful consideration.

Today, over a thousand products are used as excipients, with structures that vary from simple molecules that differ functionally to polymeric complexes of high molecular weight. Of these, not more than two hundred are described in the Pharmacopoeial monographs. It is therefore to be hoped that the Pharmacopoeias may be brought up to date as quickly as possible, both by including new, widely-used, materials and by up-dating the relative testing methods. The inclusion of an excipient in a Pharmacopoeia in any case facilitates the registration of a medicinal product and may also contribute in part towards the improvement of its final quality. Paradoxically, the characterisation of an excipient includes some tests that are not required for active principles. In fact, chemical analyses of the purity and chemical and physical tests of the material are not enough: testing of the physical behaviour during the manufacturing process phase, that is to say, the manufacturability, is also necessary.

Today, high-resolution analytical techniques are available that are not always destructive and permit the study of the behaviour of materials in the solid state, at the level of the molecule, the particle and the aggregate, thus enabling one to discern between different batches that are chemically equivalent. Naturally, the formulation technician will activate only those tests that are indispensable to improve stability, manufacturability and absorption of the pharmaceutical dosage form under consideration.

The international harmonisation of testing methods and standards now under way will facilitate his task (especially as regards the physical tests). Harmonisation obviously does not mean unifying the characteristics of the excipients because these may be produced with different characteristics. It is the technician who will decide which type and grade will best guarantee reliability and repeatability in the manufacturing phase as well as the efficacy and stability of the medicinal product. In Table 10 there is a list of the most important properties that the ideal excipient should have, in accordance with what has been said above. One point that deserves particular attention is the 'master file' as the producer's contribution to guaranteeing the quality not only of the active principles but also of the excipients. This contribution becomes essential when there is no corresponding monograph in, for example, the European Pharmacopoeia, with the relative *Certificate of Suitability* [52].

Table 10
Characteristics of an ideal excipient

Pharmaco toxicologically inactive
Chemically and physically inert vs. the drug
Compatible with other formulation ingredients
Colourless and tasteless
High fluidity or flowability
High compressibility
Available world-wide from many sources and inexpensive
Well characterised by suppliers, i.e. master file
Easy to store
Lot-to-lot reproducible
Performance consistent with the specific dosage form

What has been said here lays no claim to being new to those who are involved in the day-to-day formulation and manufacture of medicinal products. The intention was and is to take another look at how and with what care the functions and functionality of excipients should be interpreted today and at the new tendencies in the development of the excipients of the 21st century [53,54]. Only on this basis will it be possible in the near future to design and launch on the market new materials with physicomechanical and biopharmaceutical characteristics that meet the growing demands of the pharmaceutical manufacturing industry and permit the more rational development of really innovative pharmaceutical dosage forms and therapeutic systems.

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